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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,272	11/22/2004	Domenico Maglione	10500-008	4002

29391 7590 03/27/2006

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EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/507,272	MAGLIONE ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received January 19, 2006. Claims 16-35 are pending and currently under examination.

The priority date is March 5, 2002.

Withdrawal of Objections and Rejections

The indicated allowability of claims 23-29 are withdrawn in view of new rejections which are indicated below.

The rejection of claims 16-22 under 35 U.S.C. 103(a) as being unpatentable over Ziche et al. (1997 Laboratory Investigation 76(4): 517-531) in view of Failla et al. (2000 J. Invest. Dermatology 115(3): 388-395) is withdrawn. However, new rejections under 35 U.S.C. 102(b) as being unpatentable over Ziche et al. and Carmeliet et al. are made in this current Office action to claims 16-22 and 27.

Maintenance of Objections and Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 30-35 are rejected again under 35 U.S.C. 103(a) as being unpatentable over Carmeliet et al. (WO 0156593). Carmeliet et al. teach enhanced revascularization of acute myocardial infarcts by administration of PLGF-1 (p. 17). In working example 3,

Carmeliet et al. show the treatment of infarcted mice with PLGF dimer with different dosage units of 715 ng/day and 3.5 ug/day, respectively (p. 18, line 10). Carmeliet et al. also disclose dosages of PLGF composition that can be administered. For example, examples of therapeutically effective amounts of PLGF composition are preferably an amount of about 2 to 2,000 ug per kg of body weight of mammal to be treated. Therefore, depending on the body weight of the subject to be treated, the amount of PLGF-1 administered can vary. On pages 10-13, Carmeliet et al. also disclose various suitable pharmaceutical carriers, surfactants, and agents that can be used to formulate various forms of PLGF-1 compositions, such as solutions, emulsions, pellets, and powders. Furthermore, the PLGF-1 compositions can be administered by various means including oral, intranasal, or parenteral administration (p. 9 line 25). Carmeliet et al. do not teach PLGF-1 to be in a composition in an amount from 50 ug to 30 mg per unitary dose and/or in an amount from 0.1 mg to 10 mg per gram for topical use.

It would have been obvious to a person having ordinary skill in the art to formulate a composition comprising PLGF-1 as an active principle in dimeric form, and in an amount of about 2 to 2,000 ug per kg of body weight of subject (claims 30-35) with a suitable pharmaceutical carrier and/or agent for parenteral use or any other suitable mode of administration in view of modern pharmaceutical practice because Carmeliet et al. teach and suggest the use of compositions comprising PLGF-1 dimer as active principle for improving infarct angiogenesis and arteriogenesis.

In their remarks, Applicants assert a *prima facie* case of obviousness has not been met because the Carmeliet et al. reference does not provide the teaching, motivation, or reasoning to obtain the invention as recited in instant claims 30-35. Applicants further assert the Office action fails to articulate a reasonable explanation that leads one to achieve the respective combinations of elements in claims 30-35. Furthermore, no discussion of parenteral or topical doses are provided in Carmeliet et al., nor is there any discussion of cosmetic compositions or the recited doses of instant claims 30-35. Examiner acknowledges Applicants' remarks and will address them now. As currently written, claims 30-35 are drawn to a pharmaceutical composition comprising type 1 Placental Growth Factor (PLGF-1) and a pharmaceutically acceptable excipient. Regardless of its intended use, in this instance for parenteral use or for topical use as a cosmetic agent, claims 30-31 are still drawn to a composition comprising PLGF-1 and an acceptable excipient. Carmeliet et al. disclose compositions comprising PLGF-1 in dimeric form and disclose dosage values that encompass the values recited in the instant claims.

Applicants also assert Carmeliet et al. does not provide specific limits of the composition it used, therefore, it is speculative as to what the properties of the PLGF-1 used in Carmeliet et al. are. As currently written, instant claims 30-31 recite the element wherein at least 98.5% of the PLGF-1 is in active dimeric form and multimeric form, at least 70% is in dimeric form and no more than 1.5% is in monomeric form. However, as explained above, Carmeliet et al. describe the treatment of infarcted mice with PLGF dimer (p. 18, line 10). As disclosed in their treatment of infarcted mice, it would appear

Carmeliet et al. knew the properties of the PLGF-1 composition they were using because they disclosed it as PLGF dimer, which one of ordinary skill in the art would interpret as a composition comprising of all PLGF dimers, and therefore meets the element of claims 30-31 which recites that at least 70% of the PLGF is in dimeric form and no more than 1.5% is in monomeric form.

Applicants further assert the amount of PLGF for unitary dosage according to the present invention is higher than the amount indicated by Carmeliet et al. Applicants present the instance for a patient of 60 kg would be administered 120 ug to 120 mg per week or, for a daily unitary dosage, about 17 ug to 17 mg per daily dose. These dosages, however, still fall within the values of 50 ug to 30 mg per unitary dose or from 0.1 mg to 10 mg per gram, as recited in claims 30-31. Applicants assert since Carmeliet et al. disclose its dosages using an osmotic pump (p. 14 line 3), it is not proper to directly equate the daily doses using this to a single parenteral dose as claimed herein. However, Carmeliet et al. disclose the PLGF compositions may be provided to the patient by various routes of administration, including oral, intranasal, subcutaneous, intramuscular, intradermal, intravenous, or parenteral administration (p. 9, lines 22-25). Therefore, regardless of the type of formulation, its intended use or route of administration, Carmeliet et al. still disclose dosages of PLGF composition that lie within the unitary dosages of the present invention.

New Objections and Rejections

The disclosure is objected to because of the following informalities: the priority data needs to be updated.

Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-26, 28-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 23-26, 28-29 are drawn to a method of use of type 1 Placental Growth Factor (PLGF-1) comprising administering to adult individuals PLGF-1 to promote cutaneous or subcutaneous angiogenesis in the prevention and cosmetic treatment of natural skin aging. To recite the prevention of a process or event from happening is to guarantee without a doubt that the process or event will never occur. In example 7 of the instant specification, Applicants disclose the topical application of PLGF-1 to the left hand of healthy adult individuals ranging from 50-60 years old (p. 14-15). At a macroscopic level, the treatment yielded a general improvement of skin tone and

appearance (p. 15, line 15) and PLGF-1 was found effective against skin aging (p. 15, line 27). As disclosed by Applicants' own specification, while it appears PLGF-1 can be administered to reduce natural skin aging and improve general skin tone and appearance, it is not enabled to prevent natural skin aging completely.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16-22, 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Carmeliet et al. (WO 156593). In working example 3, Carmeliet et al. teach infarcted mice were treated with PLGF dimer with different dosage units of 715 ng/day and 3.5 ug/day, respectively (p. 18, line 10). Therefore, a method of preparing a medicament comprising PLGF was performed prior to the actual administration and is anticipated by Carmeliet et al. (claim 16). The intended use of this composition does not alter the method of preparation used by Carmeliet et al. (claims 17-22, 27).

Claims 16-22, 27, 30-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Ziche et al. (1997 Lab. Invest. 76(4): 517-531). Claims 16-22, 27, 30-35 were previously rejected under 35 U.S.C. 102(b) as being anticipated by Ziche et al. in the May 20, 2005 Office action. The rejections were subsequently withdrawn in the

October 20, 2005 Office action. However, upon reconsideration of the instant claims, Ziche et al. is deemed to be an appropriate reference under 35 U.S.C. 102(b). As currently written, claims 16-22, 27 are directed to a method of preparing a medicament comprising PLGF-1. On page 518, paragraph 2, Ziche et al. teach purification of PLGF-1 to homogeneity. This composition was used in *in vivo* assays (p. 518, paragraph 3). Therefore, a method of preparing a medicament comprising PLGF-1 is anticipated by Ziche et al. (claim 16). The intended use of this composition does not alter the method taught by Ziche et al. (claims 17-22, 27).

Ziche et al. teach PIGF-1 protein was purified mostly as homodimeric glycosylated protein and was approximately 0.17 mg/l of conditioned medium (p. 528; claim 30-35). Densitometric scanning of the stained gels revealed that 0.4%, 86.3%, and 13.2% of the total protein corresponded with monomeric, dimeric, and trimeric forms of PIGF-1, respectively (p. 518; claim 30-35). On page 528, col. 2, Ziche et al. teach affinity-purified PLGF-1 antibodies were obtained from the immune rabbit serum as described by Maglione et al. (1991 PNAS 88: 9267-9271). As described in the Maglione et al. reference, two rabbits were immunized with a total of 300 ug antigen, therefore meeting the dosage requirements of claims 30-31 (p. 9268 Maglione et al.). Statements of intended use or purpose are not limiting to the interpretation; therefore, regardless of claims 30-31 recitation of a pharmaceutical composition comprising PLGF-1 for parenteral use or topical use or a cosmetic composition comprising PLGF-1, the instant claims are still anticipated by Ziche et al. because Ziche et al. teach a pharmaceutical composition comprising PLGF-1 in active dimeric and multimeric form

as recited in the instant claims, that was suitable for administration to rabbits in a dosage unit as recited by the instant claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is 571-272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen Cochrane Carlson PhD

March 19, 2006

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER